PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C07d.

COMPLETE SPECIFICATION

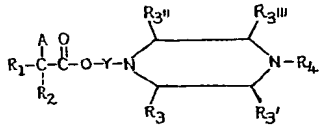
Piperazino Compounds

We, LAKESIDE LABORATORIES INC., a corporation organized under the laws of the State of Wisconsin, United States of America, of 1707 East North Avenue, Milwaukee 1, Wisconsin, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to piperazine derivatives. More particularly it is concerned with disubstituted glycolates of 4-substituted piperazine alkanols, and methods of preparation thereof.

In this specification "lower" is equivalent to "containing up to eight carbon atoms".

The present invention provides a compound of the formula



and non-toxic acid addition and quaternary ammonium salts thereof wherein in each occurrence R_1 and R_2 are phenyl, lower alkyl phenyl, halophenyl, lower alkoxy - phenyl and alkylene - dioxyphenyl, thienyl, furyl, pyridyl or cycloalkyl, and when R_1 and R_2 are phenyl they may be joined by a carbon to carbon bond in the 2-position, and wherein R_2 is furyl, R_1 can be propyl, R_3, R_3', R_3'' and R_3''' are each hydrogen or a lower alkyl group, R_4 is a lower alkyl, aralakyl, aryl, aralkenyl or alkenyl group or an alkoxy- or halo-substituted aralkyl group, A is hydroxy or halogen, Y is a lower alkylene group, and when both R_1 and R_2 are phenyl, R_1 and Y are not methyl and ethylene, respectively.

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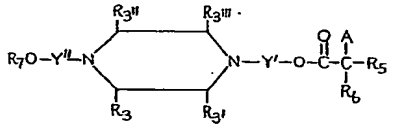
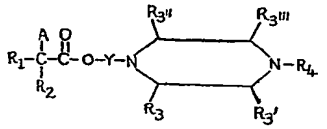
The invention further provides a member of compounds of the formula

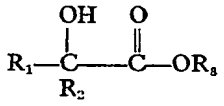


and acid addition salts thereof, wherein R_5 is a phenyl, thienyl, pyridyl or cyclohexyl group, R_6 is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_3, R_3', R_3'' and R_3''' are each hydrogen or lower alkyl, R_7 is hydrogen, an acyl or benzyl group, A is hydroxy or halogen, and Y^1 and Y^{11} are lower alkylene groups of at least two carbons each.

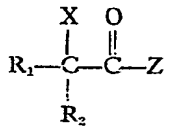
The invention still further provides the process of preparing a compound of the formula



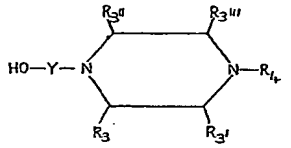
which comprises reacting a compound of the formula



or

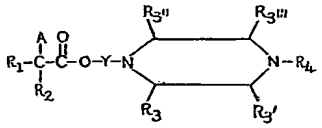


with a compound of the formula

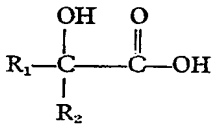


wherein R_3 is lower alkyl, X is halo and Z is a reactive halogen and if required, including the step of hydrolyzing the reaction product to form the hydroxy derivative when A is a halogen.

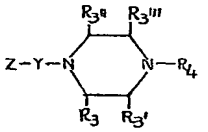
The present invention further provides the process of preparing a compound of the formula



which comprises reacting a compound of the formula

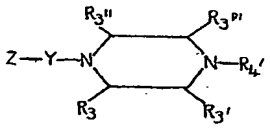


with a compound of the formula



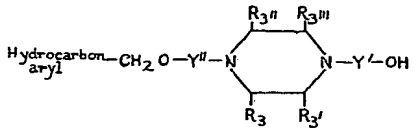
wherein Z is a reactive halogen.

The invention further provides the process which comprises reacting a compound of the formula

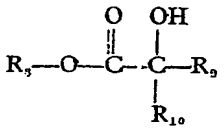


with 9 - hydroxyfluorene - 9 - carboxylic acid or a lower alkyl ester thereof wherein Z is a reactive halogen, and R_4' is a lower alkyl, aralkyl, hydroxyalkyl, acyloxyalkyl, acyloxy - alkoxyalkyl, hydroxyalkoxyalkyl, alkoxyalkyl, benzyloxy - alkoxyalkyl or benzyloxyalkyl group and when the lower alkylester thereof is used R_4' may be acyloxyalkyl and may not be hydroxyalkyl except that the hydroxy groups on the hydroxyalkyl group are esterified or etherified to block it during the reaction and subsequently regenerated.

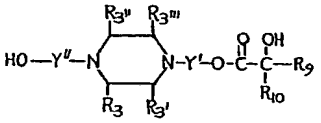
The invention further provides the process which comprises reacting a compound of the formula



with a compound of the formula

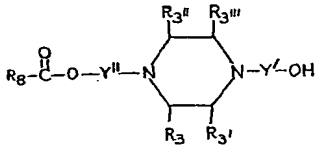


and catalytically hydrogenation the compound produced to produce a compound of the formula

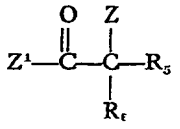


wherein in each occurrence R_9 is a phenyl, thienyl, pyridyl or cyclohexyl group, R_{10} is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_8 is a lower alkyl group, and Y^1 and Y^{11} are lower alkylene groups of at least two carbons each.

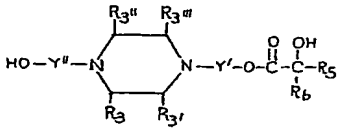
The invention further provides the process which comprises reacting a compound of the formula



with a compound of the formula



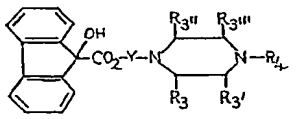
and hydrolyzing the compound formed thereby to produce a compound of the formula



wherein, in each occurrence, R_3, R_3', R_3'', R_3''' are hydrogen or a lower alkyl group, R_5 is a phenyl, thienyl, pyridyl or cyclohexyl group,

R_6 is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_8 is a lower alkyl group, Z and Z^1 are reactive halogens and Y^1 and Y^{11} are lower alkylene groups of at least two carbons each.

One of the classes of compounds included in the foregoing wherein R_1 and R_2 are phenyl and are joined by a bond connecting the ortho carbon of each phenyl ring are the novel piperazinoalkyl esters of 9 - hydroxyfluorene - 9 - carboxylic acid of the formula



wherein Y is a lower straight or branced alkylene chain of at least 2 carbons and advisably of not more than 5 carbon atoms, R_3, R_3', R_3'' and R_3''' are each hydrogen or lower alkyl, and particularly methyl, and R_4 has the significance previously assigned and is preferably an alkyl group such as methyl, ethyl, propyl, isopropyl and butyl, an aralkyl group and particularly a phenyl - lower alkyl group or nuclear-substituted phenyl-lower alkyl group such as benzyl, phenylethyl, *p* - chlorophenylpropyl and *p* - methoxyphenylbutyl, a hydroxyalkyl group in which the alkyl group has at least 2 carbons such as hydroxyethyl, gamma-hydroxypropyl, 4 - hydroxybutyl and beta - hydroxypropyl, or a hydroxyalkoxy alkyl group in which the alkyl group contains 2 carbons between the piperazine ring and the ether oxygen such as hydroxyethoxyethyl

$$(—CH_2CH_2OCH_2CH_2OH)$$

and hydroxyethoxypropyl, an acyloxyalkyl group such as the acetoxyethyl and acetoxypropyl groups, an acyloxyalkoxyalkyl group such as the acetoxyethoxyethyl group, or a benzyloxyalkyl group such as the benzyloxyethyl group or a benzyloxyalkoxyalkyl group such as the benzyloxyethoxyethyl group, and nontoxic acid addition salts thereof.

The new compounds, advisably in the form of nontoxic acid addition salts, exert a pronounced psychotherapeutic effect when administered to animals, and particularly humans. The compounds induce a feeling of relaxation and a relief from anxiety or restlessness. In particular 4 - methylpiperazino - 2 - propyl benzilate dihydrochloride is an antihallucinatory, and an antipsychotic and calming agent. The quaternary ammonium salts of the compounds also have antispasmodic activity. Those compounds in which R_4 is methyl are of much greater activity as psychotherapeutics than the ethyl and higher alkyl derivatives. The compounds of this invention in which Y is a branched alkylene are more potent as psychotherapeutics and have lower anticholinergic side effects than compounds in which Y is a straight chain alkylene group between the piperazino portion and the glycolate portion.

The new compounds also form salts with penicillin and thus may be used to isolate penicillin from fermentation broths and other solutions of this antibiotic.

While the main activity of the compounds of this invention is psychotherapeutic, these compounds also exert secondary activities. For example, 1 - methyl - 4 - piperazinopropyl benzilate is a mild stimulant. Methoxylation or methylation of one of the phenyl rings of either of these compounds gives compounds that have pronounced central stimulant properties. Thus, 1 - methyl - 4 - piperazino - propyl 2^1 - methylbenzilate and 1 - methyl - 4 - piperazinoethyl 4^1 - methoxybenzilate are pronounced central stimulants. As compared to this, however, 1 - methyl - 4 - piperazino - propyl 4^1 - chlorobenzilate and 1 - methyl - 4 - piperazinoethyl 3^1 - chlorobenzilate have sedative effects. Thus, the introduction of a chloro substituent into one of the phenyl rings produces a sedative effect.

Some of the disubstituted glycolic acids which may be used in the foregoing processes in the form of lower alkyl esters are methyl benzilate, methyl phenylcyclohexyl glycolate, ethylphenylcyclopentyl glycolate, methyl 2 - thienyl phenyl glycolate, ethyl phenyl propyl glycolate, methyl dicyclohexyl glycolate, ethyl *p* - chlorophenyl furyl glycolate, methyl *p* - methoxyphenyl - 3 - pyridyl glycolate, methyl 4 - chlorobenzilate, methyl 2 - methylbenzilate, methyl 4 - methoxybenzilate, methyl 3 - chlorobenzilate, methyl 3,4 - dimethoxybenzilate, methyl 3,4,5 - trimethoxybenzilate and methyl 3,4 - methylenedioxybenzilate.

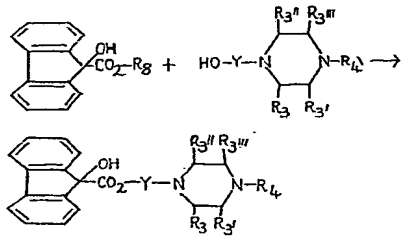
Some of the 4 - substituted piperazino alkanols which may be used in the foregoing processes are 4 - methylpiperazino propanol, 4-ethylpiperazinopropanol, 4 - ethylpiperazinoethanol, 4 - methylpiperazinoethanol, 4-propylpiperazinobutanol, 4 - isopropylpiperazino - butanol, 2 - methyl - 4 - methylpiperazinopropanol, 2 - propyl - 4 - propylpiperazinobutanol, 4 - allylpiperazino - 2^1 - propanol, 4-cinnamylpiperazinoethanol, 4 - phenylpiperazino - 3^1 - butanol, 4 - benzylpiperazino - 2^1-butanol, 4 - *p* - methoxyphenylethylpiper - azino - 4^1 - pentanol, 4 - phenylpropylpiperazino - 2^1 - propanol, 2 - methyl - 4 - cinnamylpiperazino - 3^1 - butanol, 4 - methyl - piperazino - 2^1 - propanol, 4 - ethylpiper - azino - 1^1 - ethanol, 4 - propylpiperazino - 3^1 - butanol, 4 - isopropylpiperazino - 2^1 - butanol, 2 - methyl - 4 - methylpiperazino - 2^1 - propanol, and 2 - propyl - 4 - propyl - piperazino - 3^1 - butanol.

Reaction between the lower alkyl disubstituted glycolate and the 4 - substituted piperazino alkanol is conveniently effected by bringing the reactants together in a suitable inert solvent in the presence of sodium or a sodium alkoxide. Solvents such as *n*-heptane, toluene,

xylene or an excess of the piperazino alkanol may be used for the reaction medium. The mixture is generally heated to promote the reaction with the reflux temperature being preferred. As the reaction proceeds, the lower alcohol which is formed in the reaction is distilled off. The reaction is considered completed when low boiling alcohol ceases to distil off. The product is recovered by acidifying the reaction mixture, evaporating to dryness, taking the residue up in water, adding a base such as caustic soda to the aqueous solution and extracting with an immiscible solvent. The extract may then be dried and the product recovered by distillation.

Representative of the products which are produced in this way are 4 - methylpiperazinopropyl benzilate, 4 - ethyl - piperazinoethyl benzilate, 4 - propylpiperazinobutyl benzilate, 4 - methylpiperazinopropyl phenylcyclohexyl glycolate, 4 - methylpiperazinopropyl phenylcyclopentyl glycolate, 4 - methylpiperazinopropyl phenyl 2^1 - thienyl glycolate, 4 - methylpiperazinopropyl phenyl 3^1 - chlorophenyl glycolate, 4 - methylpiperazinopropyl furyl propyl glycolate, 4 - methylpiperazinopropyl furyl 2^1 - thienyl glycolate, and 2-methyl - 4 - methylpiperazinopropyl benzilate, 4 - isopropylpiperazinoethyl benzilate, 4-phenylpiperazino - 2^1 - propyl benzilate, 4-benzyl - piperazinoethyl benzilate, 4 - allylpiperazino - 3 - butyl benzilate, 4 - cinnamylpiperazino - 2^1 - propyl phenylcyclohexyl glycolate, 4 - phenylethylpiperazino - 2^1 - propyl phenylcyclopentyl glycolate, 4 - phenylpropylpiperazinoethyl phenyl 2^1 - thienyl glycolate, 4 - allylpiperazinopropyl phenyl 3^1 - chlorophenyl glycolate, 4 - benzylpiperazino - 2^1-propyl furyl propyl glycolate, 4 - phenylpropyl - piperazino - 2^1 - propyl furyl 2^{11}-thienyl glycolate, 2 - methyl - 4 - allylpiperazino - 2^1 - propyl benzilate, 4 - methylpiperazino - 2^1 - propyl benzilate, 4 - ethyl - piperazino - 1^1 - ethyl benzilate, 4 - propylpiperazino 3^1 - butyl benzilate, 4 - methylpiperazino - 2^1 - propyl phenylcyclohexyl glycolate, 4 - methylpiperazino - 2^1 - propyl - phenylcyclopentyl glycolate, 4 - methylpiperazino-2^1 - propyl phenyl 2^{11} - thienyl glycolate, 4-methylpiperazino - 2^1 - propyl phenyl 3^{11}-chlorophenyl glycolate, 4 - methylpiperazino-2^1 - propyl furyl propyl glycolate, 4 - methylpiperazino - 2^1 - propyl furyl 2^{11} - thienyl glycolate, and 2 - methyl - 4 - methylpiperazino - 2^1 - propyl benzilate.

When R_1 and R_2 are phenyl and are joined by a carbon to carbon bond in the 2-position the following reaction produces piperazinoalkyl esters of 9 - hydroxyfluorene 9 - carboxylic acid.



wherein R_3, R_3', R_3'', R_3''', R_4, R_8 and Y have the significance previously assigned except that the hydroxy groups on the hydroxyalkyl and hydroxyalkoxyalkyl groups are previously either esterified or etherified to block them during the reaction.

Representative of the lower alkyl esters of 9 - hydroxy - 9 - fluorenecarboxylic acid which may be so reacted are the methyl ethyl and propyl esters of 9 - hydroxy - 9 - fluorenecarboxylic acid.

Some of the piperazinoalkanols which may be employed in the process are 1 - methyl-4 - piperazinopropanol, 1 - methyl - 4 - piperazinoisopropanol, 1,2 - dimethyl - 4 - piperazinoethanol, 1,2,5 - trimethyl - 4 - piperazinoamyl alcohol, and 1 - phenylisopropyl - 4-piperazinoethanol.

Some of the compounds prepared in accordance with this embodiment of the invention are 1^1 - methyl - 4^1 - piperazinopropyl - 9-hydroxy - 9 - fluorene carboxylate, 1^1-methyl-4^1 - piperazinoisopropyl - 9 - hydroxy - 9-fluorene carboxylate, $1^1,2^1$ - dimethyl - 4^1-piperazinoethyl - 9 - hydroxy - 9 - fluorene carboxylate, $1^1,2^1,5^1$ - trimethyl - 4^1 - piperazinoethyl - 9 - hydroxy - 9 - fluorene carboxylate, and 1^1 - phenylisopropyl - 4^1 - piperazinoethyl - 9 - hydroxy - 9 - fluorene carboxylate.

Those compounds in which R_4' is a protected hydroxyalkyl or hydroxyalkoxyalkyl may be converted to the free alcohols by hydrolysis e.g. of a protecting ester group such as the acetoxy group, or by catalytic reductive cleavage e.g. of a protecting benzyloxy group using for example palladium on charcoal as the catalyst and hydrogen at 2 to 5 atmospheres of pressure and at about 20 to 80° C. in a lower alcohol.

An alternative method of producing any of the above compounds wherein the glycolate substituents are both aryl, comprises reacting a di-aryl substituted halo or acyloxy acetyl

halide with a 4-substituted piperazino alkanol to produce an intermediate 4 - substituted piperazinoalkyl di-aryl substituted halo or acyloxy acetate which is subsequently hydrolyzed to the corresponding 4-substituted piperazinoalkyl di-aryl substituted glycolate.

Representative di - aryl substituted halo or acyloxy acetyl halides which may be used are diphenylchloroacetyl chloride, phenyl 2-thienyl chloroacetyl chloride, diphenyl acetoxy acetyl chloride and 3 - pyridyl *p* - chlorophenyl chloroacetyl chloride.

4-Substituted piperazino alkanols such as those previously named may also be used.

In the first step of this process the reactants may be conveniently brought together in an inert organic solvent such as benzene, toluene, isopropanol, or acetone. An acid acceptor such as triethylamine is generally included in the reaction mixture. Elevated temperatures up to the reflux temperature are generally employed to enhance the rate of reaction and maintain solubility of the reactants. The reaction product may be recovered from the mixture by conventional methods.

Some of the compounds which are produced in this way are 4 - methylpiperazinopropyl diphenylchloroacetate, 4 - ethylpiperazinobutyl phenyl 2^1 - thienyl chloroacetate, 4-isopropylpiperazinopropyl phenyl 3^1 - pyridyl chloroacetate, 2 - methyl - 4 - methylpiperazinopropyl diphenylchloroacetate, 4 - benzylpiperazino - 2^1 - propyl diphenylchloroacetate, 4 - phenylpiperazino - 3^1 - butyl phenyl 2^1 - thienyl chloroacetate, 4 - phenylethylpiperazino - 2^1 - propyl phenyl 3^{11} - pyridyl chloroacetate, 2 - methyl - 4 - phenylpropylpiperazino - 2^1 - propyl diphenylchloroacetate, 4-methylpiperazino - 2^1 - propyl diphenylchloroacetate, 4 - ethylpiperazino - 3^1 - butyl phenyl 2^{11} - thienyl chloroacetate, 4 - isopropylpiperazino - 2^1 - propyl phenyl 3^{11}-pyridyl chloroacetate, and 2 - methyl - 4-methylpiperazino - 2^1 - propyl diphenylchloroacetate.

These and other compounds are readily hydrolyzed to the corresponding 4-substituted piperazinoalkyl di - aryl substituted glycolate, advisably in the presence of a mineral acid and preferably hydrochloric acid. This hydrolysis may also be readily effected in the animal body.

The compounds also may be conveniently produced by reacting a disubstituted glycolic acid with an appropriate 4 - alkyl piperazino alkyl halide.

The reactants used in this process are essentially the same as those named previously except that the free glycolic acid is used plus a 4 - substituted piperazinoalkyl halide instead of the corresponding alkanol. The reaction is readily effected by combining the reactants in an inert solvent such as isopropanol and heating the mixture at an elevated temperature, such as the reflux temperature.

Other compounds, for example 4 - [3 - (2-phenylpropyloxy) propyl] piperazinoethanol, 4 - {5 - [4 - (2 - thienyl butyloxy)]pentyl} piperazinopropanol and 4-(3-benzyloxypropyl) piperazinobutanol may be conveniently produced by reacting a lower alkyl ester of a disubstituted glycolic acid with a 4 - aralkyloxyalkylpiperazinoalkanol in the presence of an alkaline condensation catalyst such as sodium or sodium methoxide to produce the corresponding 4 - aralkyloxyalkylpiperazinoalkyl glycolate which is then subjected to reductive cleavage to produce the hydroxyalkylpiperazinoalkyl glycolate.

Rrepresentative of the disubstituted glycolic acid esters which may be used are lower alcohol esters of benzilic acid, phenylcyclohexyl glycolic acid, phenylcyclopentyl glycollic acid, 2 - thienyl phenyl glycolic acid, dicyclohexyl glycolic acid, furyl phenyl glycolic acid, 3-pyridyl phenyl glycolic acid, and di - 2-thienyl glycolic acid.

Some of the 4 - aralkyloxyalkylpiperazinoalkanols which may be used in the process are 4 - (2 - benzyloxyethyl)piperazinoethanol, 4-(4 - benzyloxybutyl)piperazinopropanol, and 4 - (3 - benzyloxypropyl)piperazinoethanol.

The first step of the reaction is conveniently effected by bringing the reactants together in a nonreactive solvent such as *n* - heptane, methylcyclohexane, benzene, toluene or xylene. An excess of the 4 - benzyloxyalkylpiperazinoalkanol may also be used as the reaction media. Elevated temperatures such as the reflux temperature are generally employed to increase the reaction rate. As the reaction proceeds, the low boiling alcohol formed in the ester interchange reaction is removed by distillation. After the theoretical amount of alcohol is collected the reaction is considered completed. The desired product may be conveniently recovered from the mixture by conventional means such as by fractional distillation.

Some of the products produced in this way are 4 - (2 - benzyloxyethyl)piperazinoethyl benzilate, 4 - (3 - benzyloxypropyl)piperazinopropyl 2^{11} - thienyl 3^{111} - pyridyl glycolate, 4 - (2 - benzyloxyethyl) piperazinoethyl 2^1 - furyl phenyl glycolate, 4-(2-benzyloxyethyl)piperazinoisopropyl phenylcyclohexyl glycolate, 4 - (2 - benzyloxyethyl) piperazinoethyl phenyl 2^1 - thienyl glycolate, and 4 - (2 - benzyloxyethyl)piperazinoethyl ethyl phenyl glycolate.

The benzyloxy group is cleaved from these and other compounds within the scope of this invention by the use of catalytic hydrogenation. Palladium - on - charcol is a particularly satisfactory catalyst. A lower alcohol such as ethanol may be used as the hydrogenation medium. Low hydrogen pressures of 2 to 5 atmospheres and temperatures of 20 to 80° C. are suitable for effecting the cleavage. The hydrogenation may be considered completed when hydrogen uptake has ceased. Recovery

of the product may be readily achieved by filtering off the catalyst, distilling off the solvent and crystallizing the residue from a suitable solvent such as ether.

Representative of the compounds produced in this way are 4 - (2 - hydroxyethyl)piperazinoethyl benzilate, 4 - hydroxyethyl piperazinoethyl phenylcyclohexyl glycolate, 4 - (3-hydroxypropyl)piperazinopropyl 2^1 - thienyl 3^{11} - pyridyl glycolate, 4 - (2 - hydroxyethyl) piperazinoethyl 2^1 - furyl phenyl glycolate, 4-(2 - hydroxyethyl)piperazinoisopropyl phenylcyclohexyl glycolate, 4 - (2 - hydroxyethyl) piperazinoethyl phenyl 2^1 - thienyl glycolate, and 2 - methyl - 4 - (2 - hydroxyethyl)piperazinoethyl benzilate.

According to an additional process, some of the compounds may be conveniently prepared by reacting a 4 - acyloxyalkyl piperazinoalkanol with an alpha - halo - disubstituted acetyl chloride to produce the corresponding 4-acyloxyalkyl piperazinoalkyl - alpha - halo - (disubstituted)acetate ester which is then hydrolyzed to the hydroxyalkyl piperazinoalkyl glycolate.

A few of the 4 - acyloxyalkylpiperazinoalkanols which may be used in this process are 4 - (2 - acetoxyethyl)piperazinoethanol, 4-acetoxymethylpiperazinomethanol, 4 - (4-acetoxybutyl)piperazinopropanol, 4 - (3 - acetoxypropyl)piperazinoethanol and 2 - methyl - 4-(2 - acetoxyethyl)piperazino piperazinoethanol.

Some of the alpha - halo - (disubstituted) acetyl halides which may be used in the process are diphenylchloroacetyl chloride, 2 - thienyl phenyl chloroacetyl bromide, di - 3 - pyridylchloroacetyl chloride, di - 2 - thienylchloroacetyl chloride, and phenyl - 3 - pyridylchloroacetyl chloride.

In the first step of this alternative process the reactants are conveniently brought together in an inert organic solvent such as toluene, isopropanol and acetone. An acid acceptor such as triethylamine is generally included in the reaction mixture to remove the hydrohalic acid formed in the reaction. Elevated temperatures up to the reflux temperature are generally employed to enhance the rate of reaction and maintain solubility of the amino alcohol. Following reaction, the mixture may be worked up according to conventional methods to recover the desired 4 - acyloxyalkyl piperazinoalkyl - alpha - halo - (disubstituted)acetate ester.

Typical of the compounds which are produced in this way are 4^1 - (2 - acetoxyethyl) piperazinoethyl diphenyl chloroacetate, 4^1 - (3-acetoxypropyl)piperazinopropyl di - 2-thienyl bromoacetate, 4^1 - acetoxyethyl piperazinoethyl phenyl 3 - pyridyl chloroacetate and 4^1-(4 - acetoxy butyl)piperazinoethyl diphenyl chloroacetate.

Hydrolysis of these and similar compounds within the scope of this invention is readily effected with an aqueous mineral acid such as aqueous hydrochloric acid. By hydrolysis these acetoxy - haloacetates are converted to hydroxyalkyl piperazinoalkyl glycolates such as those named previously.

Acid addition salts are produced by contacting the compounds with a suitable acid such as formic acid, citric acid, maleic acid, sulfuric acid, hydrochloric acid, succinic acid, tartaric acid, benzoic acid or fumaric acid.

Quaternary ammonium salts may be formed by contacting the compounds with a suitable alkylating agent such as dimethyl sulfate or an alkyl halide such as methyl chloride or ethyl bromide.

The active agents of this invention may be administered to animals and humans as pure compounds. It is advisable, however, to first combine one or more of the compounds with a suitable pharmaceutical carrier to attain a more satisfactory size to dosage relationship.

Pharmaceutical carriers which are liquid or solid may be used. The preferred liquid carrier is water. Flavoring materials may be included in the solutions as desired.

Solid pharmaceutical carriers such as starch, sugar, and talc may be used to form powders. The powders may be used as such for direct administration to a patient or, instead, the powders may be added to suitable foods and liquids, including water, to facilitate administration.

The powders may also be used to make tablets, or to fill gelatin capsules. Suitable lubricants like magnesium stearate, binders such as gelatin, and disintegrating agents like sodium carbonate in combination with citric acid may be used to form the tablets.

Unit dosage forms such as tablets and capsules may contain any suitable predetermined amount of one or more of the active agents as a non-toxic acid addition salt and may be administered one or more at a time at regular intervals. Such forms should, however, generally contain a concentration of 0.1% to 10% and preferably 1.0%, by weight of the active agent.

The daily dosages of the active agents can be varied considerably and according to the extent of activity to be induced. In general, from about 5 to 50 mgm. daily is adequate to achieve marked psychotherapeutic activity in humans. Doses of 100—200 mgm. per day may also be administered safely and may be required in certain mental conditions. Lower dosages would generally be employed in animals smaller than humans.

The oral route of administration is advisably employed for administering the active agents of this invention.

The following examples show the preparation of specific compounds with which this invention is concerned.

EXAMPLE 1

4 - Isopropylpiperazinoethyl benzilate and its hydrochloride.

A mixture containing 0.49 mole of methyl benzilate, 0.49 mole of 1 - isopropyl - 4 - hydroxyethyl piperazine, 325 c.c. *n* - heptane and 1.2 g. of sodium methoxide was refluxed with stirring with the simultaneous removal of methanol as the reaction proceeded. When the theoretical amount of methanol had been collected, the reaction mixture was diluted with additional *n*-heptane and clarified by filtration. A gummy precipitate formed and was crystallized in water. The solid was removed by filtration, washed with cold water and dried. The yield of the basic ester was 98.4%.

The dihydrochloride salt was prepared by dissolving 0.33 mole of the basic ester in 500 c.c. of isopropyl alcohol and adding ethereal hydrochloric acid to the mixture until the solution was strongly acid (pH 2—3). The product precipitated immediately and was isolated by filtration m.p. 214° C. dec. (yield 78%).

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_3$: Cl, 15.58; N, 6.15
Found: Cl, 15.29; N, 6.21

EXAMPLE 2

4 - Methylpiperazinoethyl phenylcyclohexyl-glycolate and its dihydrochloride.

The basic ester was obtained in 81% yield by the method described in Example 1 from methyl phenylcyclohexyl glycolate and 4-methylpiperazinoethanol. The dihydrochloride salt was prepared in methanol, m.p. 232° C. (dec.), yield 64%.

Anal. Calcd. for $C_{21}H_{34}Cl_2N_2O_3$: Cl, 16.37; N, 6.46.
Found: Cl, 16.53; N, 6.41.

EXAMPLE 3

4 - Methylpiperazinoethyl dicyclohexyl glycolate

The basic ester was obtained by the method of Example 1. From 23.8 g. (0.165 mole) of 4 - methylpiperazinoethanol and 38.2 g. (0.15 mole) methyl dicyclohexylglycolate there was obtained 25 g. (45%) of the basic ester, which was a water-insoluble oil. The dihydrochloride salt was prepared in anhydrous ether with ethereal hydrochloric acid; the salt turned out to be a difficultly crystallizable oil.

EXAMPLE 4

1 - Methyl - 4 - piperazinopropyl 4[1] - chlorobenzilate and its dihydrochloride

A mixture consisting of 18.43 g. (0.116 mole) of 4 - methylpiperazinopropanol, 32.2 g. (0.116) mole of methyl 4 - chlorobenzilate, 0.7 g. of sodium methoxide and 300 c.c. of *n*-heptane was refluxed until 7.3 cc. of methanol was collected. The catalyst was filtered off, and the filtrate was washed twice with 100 cc. of water. The organic material was dried over potassium carbonate and the solvent distilled off. Yield, 45 g. (96.3%).

The base was dissolved in 250 cc. of isopropanol and acidified with ethereal hydrochloric acid. The solid was collected by filtration, washed with ether and dried, yield, 39.8 g. (75%), m.p. 203° C.

Anal. Calcd. for $C_{22}H_{29}Cl_3N_2O_3$: N, 5.98; Cl, 14.90.
Found: N, 5.90; Cl, 14.85.

EXAMPLE 5

1 - Methyl - 4 - piperazinopropyl 2[1]-methylbenzilate and its dihydrochloride

A mixture consisting of 12.4 g. (0.079 mole) of 4 - methylpiperazinopropanol, 20.1 g. (0.079 mole) of methyl 2 - methylbenzilate, 0.35 g. of sodium methoxide and 250 c.c. of heptane was refluxed until 4.7 cc. of methanol was collected. The product was isolated as described in Example 1; Yield, 27.2 g. (91%).

The hydrochloride salt was prepared as in Example 6, Yield 26 g. (80%) m.p. 210° C.

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_3$: N,6.15; Cl, 15.57.
Found: N, 6.21; Cl, 15.70.

EXAMPLE 6

1 - Methyl - 4 - piperazinoethyl 4[1] - methoxybenzilate and its dihydrochloride

A mixture consisting of 27.3 g. (0.1 mole) of methyl 4 - methoxybenzilate, 14.4 g. (0.1 mole) of 4 - methylpiperazinoethanol, 0.8 g. of sodium methoxide and 250 cc. of heptane was refluxed for five hours and 6.5 cc. of methanol were collected. The catalyst was filtered off and the filtrate was washed twice

with 100 cc. of water. The organic material was dried over potassium carbonate and the solvent was distilled. Yield, 43.15 g.

The hydrochloride salt was prepared by dissolving the base in 300 cc. of ether and acidifying with ethereal hydrochloric acid. Yield, 28.25 g. (61.8%) m.p. 204° C. (dec.).

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2O_4$: N, 6.12; Cl, 15.50.
Found: N, 5.92; Cl, 14.92.

Example 7

1 - Methyl - 4 - piperazinoethyl 3^1 - chlorobenzilate and its dihydrochloride

A mixture consisting of 27.7 g. (0.1 mole) of methyl 3 - chlorobenzilate, 14.4 g. (0.1 mole) of N - methyl - 4 - piperazinoethanol, 0.8 of sodium methoxide and 250 cc. of heptane was refluxed for six hours and 6.2 cc. of methanol was collected. The product was isolated as described in Example 6; yield, 35.4 g. (91%).

The hydrochloride salt was prepared as in Example 6; yield 19 g. (41.3%) m.p. 221—222° C. (dec.).

Anal. Calcd. for $C_{21}H_{27}Cl_3N_2O_3$: N, 6.06; Cl, 23.03.
Found: N, 6.02; Cl, 22.90.

Example 8

1 - Methyl - 4 - piperazinopropyl $3^1,4^1$-dimethoxy benzilate

This compound is prepared as described in Example 6 using methyl 3,4-dimethoxybenzilate in place of methyl 4 - methoxybenzilate.

Example 9

1 - Methyl - 4 - piperazinopropyl $3^1,4,^1,5^1$-trimethoxybenzilate

This compound is prepared as shown in Example 6 using methyl 3,4,5 - trimethoxybenzilate in place of methyl 4 - methoxybenzilate.

Example 10

1 - Methyl - 4 - piperazinopropyl $3^1,4^1$,-methylenedioxybenzilate

This compound was prepared as shown in Example 6 using methyl 3,4 - methylenedioxybenzilate in place of methyl 4 - methoxybenzilate.

Example 11

4 - Methylpiperazino - 2^1 - propanol

To 100.2 g. (1.0 mole) of methylpiperazine in 1 lt. of methanol was added 58.1 g. (1.0 mole) of propylene oxide dissolved in 100 cc. dry toluene. The reaction mixture was stirred at room temperature for several hours. The product was isolated by fractional distillation in vacuo, b.p. 60—61° C. (0.70 mm.); yield 108 g. (68%); N_D^{25} 1.4701.

Anal. Calcd. for $C_8H_{18}N_2O$: N, 17.70.
Found: N, 17.70.

4 - Methylpiperazino - 2 - propyl benzilate

A mixture containing 48.4 g. (0.20 mole) of methyl benzilate, 31.6 g. (0.20 mole) of 4-methylpiperazino-2^1-propanol, 1.3 g. sodium methoxide and 500 cc. of *n* - heptane was refluxed with stirring and the methanol formed during the reaction was separated. The sodium methoxide was removed by filtration and the filtrate washed twice with water. The solvent was removed by distillation and 55 g. (75%) of residue obtained which is the basic ester.

The residue was converted to the dihydrochloride salt in isopropyl alcohol with ethereal hydrochloric acid, yield 49.5 g. (75%); m.p. 211—212° C.

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2O_3$ Cl, 16.06; N, 6.34.
Found: Cl, 16.11; N, 6.29.

Example 12

4 - Methylpiperazino - 2^1 - propyl benzilate and its dihydrochloride

To 53.0 g. (0.20 mole) of diphenylchloroacetyl chloride in 200 cc. of dry benzene was added 31.6 g. (0.20 mole) 4 - methylpiperazino - 2^1 - propanol in 100 cc. of benzene and 20 cc. of triethylamine. The mixture was stirred and refluxed for two hours, the triethylamine hydrochloride removed by filtration and the filtrate concentrated. The residual oil was taken up with dilute aqueous hydrochloric acid and refluxed for 15 minutes. Any water insoluble material was removed by ether extraction. The aqueous solution was neutralized with potassium carbonate, the benzilate ester extracted with ether and the ether extracts dried with potassium carbonate. The ether was removed by distillation and the basic ester converted to the dihydrochloride ester, m.p. 210—211° C. Mixed m.p. with product obtained from Example 11 was 211—212° C., yield 40 g.

Example 13

4 - Phenylpiperazinoethyl benzilate and its hydrochloride

A mixture containing 41.3 g. (0.20 mole) of 4-phenylpiperazino ethanol, 48 g.. (0.20 mole) of methyl benzilate and 0.8 g. of sodium methoxide in about 500 cc. of *n*-heptane was re-

fluxed with stirring and the methanol formed during the reaction was separated. The sodium methoxide was removed by filtration and the filtrate washed twice with water. The solvent was removed by distillation and 77.5 g. (93%) of the basic ester obtained. The monohydrochloride salt melted at 200° C. dec.

Anal. Calcd. for $C_{26}H_{28}Cl_2N_2O_3$: Cl, 7.86; N, 6.21.
Found: Cl, 7.88; N, 6.21.

EXAMPLE 14

4 - Benzylpiperazinoethyl benzilate and its dihydrochloride

This compound was prepared by the method described in Example 13. From 29.1 g. (0.13 mole) of 4 - benzylpiperazino ethanol and 24.2 g. (0.10 mole) methyl benzilate, there was obtained 18.4 g. (37%) of the dihydrochloride upon acidification of the basic ester in ether, m.p. 224—225° C. dec.

Anal. Calcd. for $C_{27}H_{32}Cl_2N_2O_3$: Cl, 14.08; N, 5.56.
Found: Cl, 14.16; N, 5.46.

EXAMPLE 15

4 - Cinnamyl piperazinoethyl benzilate

4 - Cinnamyl piperazinoethanol (preliminary preparation)

To a mixture of 39.06 g. (0.30 mole) of hydroxyethyl piperazine, 41.46 g. (0.30 mole) of freshly ground anhydrous potassium carbonate and 300 cc. of ethanol, there was added dropwise with stirring 45.8 g. (0.30 mole) of cinnamyl chloride. The mixture was refluxed with stirring for 3 hours, the inorganic salts separated by filtration and the product collected at 165° C. (0.08 mm.); yield 52.5 g. (71%).

Anal. Calcd. for $C_{15}H_{22}N_2O$: N, 11.37.
Found: N, 11.26.

Preparation of 4 - Cinnamyl piperazinoethyl benzilate.

This ester was prepared by the method described in Example 13. From 28.64 g. (0.22 mole) of 4 - cinnamylpiperazinoethanol and 48.4 g. (0.20 mole) of methyl benzilate, there was obtained 49.8 g. (47%) of the compound; m.p. 201—202° C. Several recrystallizations from isopropyl alcohol raised the m.p. to 215° C. dec.

Anal. Calcd. for $C_{29}H_{34}Cl_2N_2O_3$: Cl, 13.41; N, 5.29.
Found: Cl, 13.42; N, 5.21.

EXAMPLE 16

4 - Allylpiperazinoethyl phenyl 2[1] - thienyl glycolate.

A mixture of 21.4 g. (0.10 mole) of 4-allylpiperazinoethylchloride, 23.4 g. (0.10 mole) of phenyl 2 - thienyl glycolic acid and 300 cc. of anhydrous isopropyl alcohol was refluxed for thirty hours. The isopropyl alcohol was removed by distillation in vacuo. The oily residue was dissolved in water and the aqueous solution extracted with ether. The aqueous layer was neutralized with potassium carbonate and extracted repeatedly with ether. The ether extracts were dried with potassium carbonate and concentrated. The basic ester was a high-boiling water-insoluble oil.

EXAMPLE 17

4 - Beta - acetoxyethylpiperazinoethyl diphenyl chloroacetate and its dihydrochloride.

To 34 g. (0.157 mole) of 4 - beta - acetoxyethylpiperazinoethanol in 200 cc. of benzene and 15.8 g. of triethylamine was added 41.6 g. (0.157 mole) of alpha - chlorodiphenyl acetyl chloride dissolved in 35 cc. of benzene. The mixture was stirred and refluxed for 2 hours, the triethylamine .HCl separated by filtration and the benzene removed by distillation. The residue was dissolved in acetone and converted to the dihydrochloride salt with ethereal HCl. The gummy precipitate was crystallized by adding 20 cc. of acetonitrile. The crystalline solid was filtered, m.p. 210—213° C. dec.

Anal. Calcd. for $C_{24}H_{31}N_2O_4$: Cl, 20.57; N, 5.41.
Found: Cl, 19.46; N, 5.64.

EXAMPLE 18

4 - Beta - hydroxyethylpiperazinoethyl benzilate and its dihydrochloride.

Fifty-seven gms. (0.11 mole) of the compound of Example 17 was dissolved in 300 cc. of hot water and 10 g. of activated charcoal added. The mixture was stirred at reflux temperature for ten minutes, filtered hot through a bed of Celite and the filtrate neutralized with sodium bicarbonate. The gummy base was extracted with chloroform and converted to the dihydrochloride salt by the addition of ethereal hydrochloric acid. The gummy precipitate was crystallized in ether, yield 29 g., m.p. decomposition at 170° C.

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2O_4$: Cl, 15.53; N, 6.12.
Found: Cl, 14.97; N, 6.00.

EXAMPLE 19

4 - Beta - benzyloxyethylpiperazinoethanol (preliminary preparation)

A mixture of 130 g. (1.0 mole) of 4 - hydroxyethylpiperazine and 85 g. (0.50 mole) of beta - benzyloxyethyl chloride in 500 cc. of toluene was refluxed with stirring for 5 hours. The reaction mixture was clarified by filtration and the filtrate subjected to fractional distillation in vacuo. The product was collected at 157—159° C. (0.10 mm.); yield 61.5 g.; N_D^{25} 1.5319.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: N, 10.58.
Found: N, 10.47.

4 - Beta - benzyloxyethylpiperazinoethyl benzilate and its dihydrochloride.

A mixture of 29.1 g. (0.11 mole) of beta-benzyloxyethylpiperazinoethanol, 24.2 g. (0.10 mole) methyl benzilate and 0.6 g. of sodium methoxide in 250 cc. of *n*-heptane was stirred and refluxed until no more methanol distilled over. The hot reaction mixture was clarified by filtration and the filtrate washed repeatedly with water. The organic phase was dried with potassium carbonate, filtered and the filtrate concentrated; 43 g. (91%) of a yellow oily residue remained which was converted to the dihydrochloride salt with ethereal HCl in acetone, m.p. 197—198° C.

Anal. Calcd. for $C_{29}H_{36}Cl_2N_2O_4$: Cl, 12.97; N, 5.11.
Found: Cl, 13.16; N, 5.23.

EXAMPLE 20

4 - Beta - hydroxyethylpiperazinoethyl benzilate dihydrochloride.

The dihydrochloride salt of Example 19 (30 g.) was dissolved in aqueous ethanol and subjected to hydrogenation at 60 pounds per square inch (4.21 kilograms per square centimeter) of H_2 with 1.5 g. (10%) palladium-on-charcoal at 40° C. and the product isolated by removing the catalyst, concentrating the filtrate and crystallizing the residue from anhydrous ether, m.p. 194—195° C.

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2O_4$: Cl, 15.52; N, 6.12.
Found: Cl, 15.84; N, 6.17.

EXAMPLE 21

4 - Beta - benzyloxyethylpiperazinoisopropyl phenylcyclohexyl glycolate.

From 29.1 g. (0.11 mole) of beta - benzyloxyethylpiperazinoethanol and 24.5 g. (0.10 mole) of methyl phenylcyclohexyl glycolate there was obtained 39 g. (81%) of the basic ester by the procedure described in Example 19.

EXAMPLE 22

4 - Beta - hydroxyethylpiperazinoisopropyl phenylcyclohexyl glycolate dihydrochloride.

The basic ester of Example 21 was dissolved in aqueous ethanol containing two equivalents of hydrochloric acid. The benzyl group was cleaved by catalytic hydrogenation as described in Example 20.

EXAMPLE 23

4 - Beta - benzyloxyethylpiperazinoethyl phenyl 2^1 - thienyl glycolate.

From 14.6 g. (0.055 mole) of beta-benzyloxyethylpiperazinoethanol and 12.5 g. (0.05 mole) of methyl 2 - thienyl phenyl glycolate, reacted as in Example 19, there was obtained 22 g. (92%) of the basic ester as an oil.

Anal. Calcd. for $C_{28}H_{28}Cl_2N_2O_3$: N, 6.32; Cl, 15.90.
Found: N, 6.37; Cl, 16.14.

EXAMPLE 24

4 - Beta - hydroxyethylpiperazinoethyl phenyl 2^1 - thienyl glycolate dihydrochloride.

Reductive cleavage of 25 g. of the dihydrochloride salt of the base of Example 23 in 150 cc. of 70% aqueous ethanol with 1.0 g. of 10% palladium-on-charcoal as described in Example 20 gave the hydroxyethyl derivative.

EXAMPLE 25

1^1 - Methyl - 4^1 - piperazinopropyl - 9 - hydroxyfluorene - 9 - carboxylate and its dihydrochloride.

A mixture consisting of 21.7 g. (0.09 M) of methyl - 9 - hydroxyfluorene - 9 - carboxylate, 14.2 g. (0.09 M) of N - methyl - N^1 - (3-hydroxypropyl) piperazine, 0.5 g. of sodium methoxide and 250 cc. of *n*-heptane was refluxed for six hours with 5.3 cc. of methanol was collected. The catalyst was filtered off, and the filtrate was washed twice with 100 cc. of water. The organic material was dried over potassium carbonate and the solvent was distilled off. Yield 33.1 g. (95%). The base was dissolved in 300 cc. acetone and acidified with 50 cc. of (4N) ethereal hydrochloric acid. The solid was collected by filtration, washed with acetone, and dried at 105° C., yield 32.9 g. (82%), m.p. 233—235° C. (dec.). The solid was recrystallized from methanol yield 21.7 g. (54.3%), m.p. 237° C. (dec.).

EXAMPLE 26

1^1 - Methyl - 4^1 - piperazinoisopropyl - 9 - hydroxyfluorene - 9 - carboxylate and its dihydrochloride.

A mixture consisting of 36 g. (0.15 M) of methyl 9 - hydroxyfluorene - 9 - carboxylate, 23.7 g. (0.15 M) of N - methyl - N^1 - 2 - hydroxypropyl piperazine, 0.8 g. of sodium methoxide and 375 cc. of *n* - heptane was refluxed for eight hours while 8 cc. of methanol was collected. The product was isolated as described in Example 1; yield 47 g. (85.5%). The hydrochloride salt was prepared in the same manner as in Example 25, yield 16.1 g. (24.5%), m.p. 234° C. (dec.).

Anal. Calcd. for $C_{22}H_{26}Cl_2N_2O_3$: N, 6.37; Cl, 16.14.
Found: N, 6.43; Cl, 16.27.

EXAMPLE 27

$1^1,2^1$ - Dimethyl - 4^1 - piperazinopropyl - 9-hydroxyfluorene - 9 - carboxylate.

This compound is prepared as in Example 26 by reacting methyl 9 - hydroxyfluorene-9-carboxylate with 1,2 - dimethyl - 4^1 - piperazinopropanol.

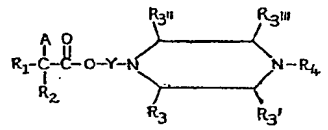
EXAMPLE 28

1^1 - Phenylisopropylpiperazinopropyl - 9 - hydroxyfluorene - 9 - carboxylate.

This compound is prepared as in Example 25 by reacting methyl 9 - hydroxyfluorene-9-carboxylate with 1 - phenylisopropylpiperazinopropanol.

WHAT WE CLAIM IS:—

1. A compound of the formula



and non-toxic acid addition and quaternary ammonium salts thereof wherein in each occurrence R_1 and R_2 is phenyl, lower alkyl phenyl, halophenyl, lower alkoxy - phenyl and alkylene - dioxyphenyl, thienyl, furyl, pyridyl or cycloalkyl groups, when R_1 and R_2 are phenyl they may be joined by a carbon to carbon bond in the 2-position and when R_2 is furyl, R_1 can be propyl, R_3, R_3', R_3'' and R_3''' is hydrogen or a lower alkyl group, R_4 is a lower alkyl, aralkyl, aryl, aralkenyl or alkenyl group, or an alkoxy- or halo - substituted aralkyl group, A is hydroxy or halogen, Y is a lower alkylene group, and when both R_1 and R_2 are phenyl, R_4 and Y are not methyl and ethylene, respectively.

2. 4 - Isopropylpiperazinoethylbenzilate.

3. 4 - Methylpiperazinoethyl phenylcyclohexyl glycolate.

4. 4 - Methyl - 4 - piperazinoethyl dicyclohexyl glycolate.

5. 1 - Methyl - 4 - piperazino - propyl 4^1-chlorobenzilate.

6. 1 - Methyl - 4 - piperazinopropyl 2^1 - methylbenzilate.

7. 1 - Methyl - 4 - piperazinoethyl 4^1 - methoxybenzilate.

8. 1 - Methyl - 4 - piperazinoethyl 3^1 - chlorobenzilate.

9. 4 - Methylpiperazino - 2^1 - propylbenzilate.

10. 4 - Lower alkyl piperazino - 2^1 - propyl benzilate.

11. 4 - Phenylpiperazinoethyl benzilate.

12. 4 - Phenyl lower alkyl piperazino-lower alkyl benzilate.

13. 4 - Phenylpiperazino - lower alkyl benzilate.

14. 4 - Phenyl lower alkyl piperazinoethyl benzilate.

15. 1^1 - Methyl - 4^1 - piperazinopropyl - 9 - hydroxyfluorene - 9 - carboxylate.

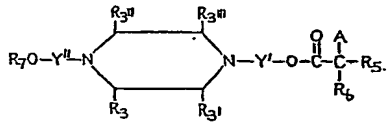
16. 1^1 - Methyl - 4^1 - piperazinoisopropyl-9 - hydroxyfluorene - 9 - carboxylate.

17. $1^1,2^1$ - Dimethylpiperazinopropyl - 9 - hydroxyfluorene - 9 - carboxylate.

18. 1^1 - Phenylisopropylpiperazinopropyl - 9 - hydroxyfluorene - 9 - carboxylate.

19. 1^1 - Lower alkyl - 4^1 - piperazino lower alkyl - 9 - hydroxyfluorene - 9 - carboxylate.

20. A member of compounds of the formula



and acid addition salts thereof, wherein R_5 is a phenyl, thienyl, pyridyl or cyclohexyl group, R_6 is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_3, R_3', R_3'' and R_3''' is oxygen or a lower alkyl group, R_7 is hydrogen, or an acyl or benzyl group, A is hydroxy or halogen, and Y^1 and Y^{11} are lower alkylene groups of at least two carbon each.

21. 4 - Beta - acetoxyethylpiperazinoethyl diphenyl chloroacetate.

22. 4 - Beta - hydroxyethylpiperazinoethyl benzilate.

23. 4 - Beta - benzyloxyethylpiperazino - ethyl benzilate.

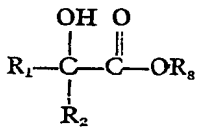
24. 4 - Beta - benzyloxyethylpiperazinoisopropyl phenylcyclohexyl glycolate.

25. 4 - Beta - benzyloxyethylpiperazinoethyl phenyl 2 - thienyl glycolate.

26. 4 - Beta - hydroxyethylpiperazinoethyl phenyl 2 - thienyl glycolate.

27. The process of preparing a compound

of the formula given in claim 1 which comprises reacting a compound of the formula



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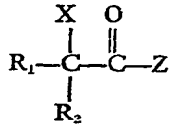
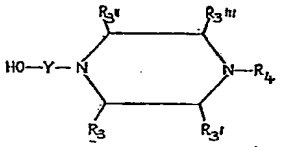
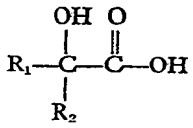


with a compound of the formula

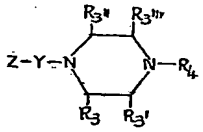


wherein R_8 is lower alkyl, X is halogen and Z is a reactive halogen and if required, including the step of hydrolyzing the reaction product to form the hydroxy derivative when A is halogen,

28. The process of preparing a compound of the formula given in claim 1 which comprises reacting a compound of the formula

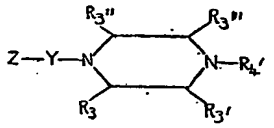


with a compound of the formula



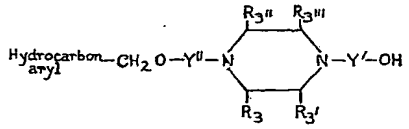
wherein Z is a reactive halogen.

29. The process which comprises reacting a compound of the formula

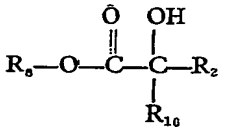


with 9 - hydroxyfluorene - 9 - carboxylic acid or a lower alkyl ester thereof wherein Z is a reactive halogen, and R_4' is a lower alkyl, aralkyl, hydroxyalkyl, acyloxyalkyl, acyloxyalkoxyalkyl, hydroxyalkoxyalkyl, alkoxylalkyl, benzyloxy-alkoxyalkyl or benzyloxyalkyl group and when the lower alkylester thereof is used R_4' may be acyloxyalkyl and may not be hydroxyalkyl except that the hydroxy groups on the hydroxyalkyl group are esterified or etherified to block it during the reaction and subsequently regenerated.

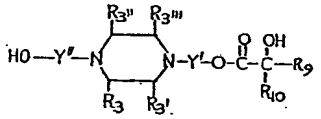
30. The process which comprises reacting a compound of the formula



with a compound of the formula

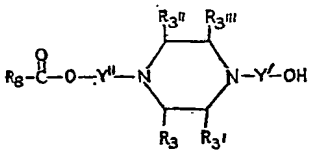


produced to produce a compound of the formula

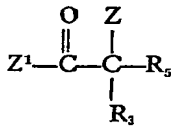


wherein in each occurrence R_9 is a phenyl, thienyl, pyridyl or cyclohexyl group, R_{10} is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_8 is a lower alkyl group, and catalytically hydrogenating the compound and Y^1 and Y^{11} are lower alkylene groups of at least two carbons each.

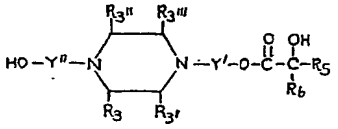
31. The process which comprises reacting a compound of the formula



with a compound of the formula



and hydrolyzing the compound formed thereby to produce a compound of the formula



wherein, in each occurrence, R_3, R_3', R_3'', R_3''' are hydrogen or a lower alkyl group, R_5 is a phenyl, thienyl, pyridyl or cyclohexyl group, R_6 is a phenyl, thienyl, furyl, cyclohexyl, cyclopentyl or lower alkyl group, R_8 is a lower alkyl group, Z and Z^1 are reactive halogens and Y^1 and Y^{11} are lower alkylene groups of at least two carbons each.

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Agents for the Applicants.

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